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Original Article

The causes of lower-extremity deep venous thrombosis in the children with cranial diseases

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Abstract: In order to investigate the prevalence of lower-extremity deep venous thrombosis (DVT) and to explore its possible reasons in children patients who received neurosurgery operation. Clinical data of 4958 cases children patients with lower-extremity DVT and without the thrombosis after the neurosurgery operation from 2010 January to 2014 December in department of neurosurgery of Tian Tan hospital were collected and analyzed. 18 cases children were diagnosed with lower-extremity DVT. All of them had invasive operation of lower-extremity deep venous catheterization. The mainly primary diseases of thrombosis children were craniopharyngioma. They have longer operation time compared with those without thrombosis ($P<0.05$). Therefore, the causes of DVT in neurosurgical children involve not only deep venous catheter-related but also neurological primary disease and operation time.

Keywords: Cranial disease, children, lower extremity deep venous thrombosis, craniopharyngioma

Introduction

Deep venous thrombosis (DVT) has low occurrence rate in children. The literatures showed that the incidence of children DVT was 5/10000 per year in the hospital, while the incidence of adult DVT was 2-2.5% [1]. However, once the DVT happens in children, he/she is prone to complication of pulmonary embolism (PE). The incidence was 16%-20%, and the mortality was 1%-4%. Children DVT is easy to recurrence, and the recurrence rate is 6.5%-21% [2, 3]. DVT induced post-thrombosis syndrome (PTS) may cause venous insufficiency, which will seriously affect children's activities and daily life [4].

Children DVT often is secondary to the application of central venous catheter (CVC) in treatment of malignant tumor, heart disease, infection, parenteral nutrition [5, 6]. Pediatric neurosurgery operation often need to use the CVC, and whether the formation of DVT in neurosurgery is caused by the factor of CVC, which is rarely reported in domestic and abroad. DVT as complication of pediatric neurosurgery is often overlooked. We collected clinic data of children who were diagnosed as the DVT in pediatric neurosurgery from January 2010 to December of 2014, which was reported as follows. We analyzed the causes of children DVT in pediatric neurosurgery and hoped that it is helpful for preventing the children DVT.

Materials and methods

General data

The cases were 4958 children patients with nervous system disease and undergone the neurosurgery operation, which included 2476 cases children patients with craniopharyngioma, in department of pediatric neurosurgery of Tian Tan hospital in China from January 2010 to December 2014. 18 cases were diagnosed asdiagnosis as lower extremity DVT, including 10 cases boys and 8 girls, aged from 2 years old to 14 years old, with an average of 7.6 years old. In addition, 40 cases children patients were randomly selected as the control from the studied cases that were not diagnosed with DVT, including 27 cases boys and 13 cases girls, aged from 2.5 years old to 17 years old, with an average of 8.7 years old.

Table 1. The annual incidence rate of DVT of pediatric department of Neurosurgery Ward

Year	The number of total children	The number of DVT children	Incidence rate (/10000)
2010	734	3	40.9
2011	750	3	40.0
2012	834	5	60.0
2013	1157	2	17.3
2014	1483	5	33.7

Table 2. The sites of DVT occurrence

	Left	Right	Bilateral
Iliac femoral vein	1	6	
The femoral popliteal vein		2	
Iliac-extensive lower extremity venous		7	2

Table 3. The classification and the proportion of primary disease in children with DVT

Neurosurgical diseases	The number of children	Proportion %
Craniopharyngioma	12	66.7*
Glioma	1	5.5
Medulloblastoma	1	5.5
Anaplastic ependymoma	1	5.5
The central cell tumor (hamartomas)	1	5.5
Mixed germ cell tumor	1	5.5
Subdural hematoma	1	5.5

*P<0.001, compared with the proportion of neurosurgery brain tumor in our hospital.

Catheter process

All selected children patients were established venous channel by CVC. CVC cathetering was generally used the method of the right femoral vein puncture, which was used for infusion, blood transfusion and anesthesia administration during operation, and should be removed after operation. 3 cases of DVT children in this study group needed long term indwelling CVC for infusion treatment. 18 cases of DVT patients were discharged from the hospital and had no hospital death.

Data collection and analysis

Symptom of DVT children patients were lower extremity edema. After diagnosis of DVT by color Doppler ultrasonography, the quantitative D-dimer was checked. The data were collected, and the incidence, primary disease, CVC catheter indwelling, operation process and laboratory examination results were analyzed by SPSS18.0 statistical package. Annual incidence rates of DVT and primary disease were compared using Fisher's exact probability test, while operation time was compared using One-way ANOVA test.

Results

The annual incidence rate of children DVT in our hospital

From 2010 to 2014, annual incidence of children DVT in department of Neurosurgery in our hospital was 36.3/10000. The annual incidence of DVT was shown in **Table 1**. There was no significant difference about the annual incidence of DVT among these years (P = 0.578), which could be calculated on the average.

The relationship between DVT and CVC

As shown in **Table 2**, DVT was occurred in children with CVC catheter indwelling in proximal or deep vein of lower extremity, which suggested that DVT was related to CVC indwelling.

The relationship between DVT and primary disease

As shown in **Table 3**, the diseases in department of neurosurgery that might cause DVT in children were mostly craniopharyngioma, accounting for 66.7%, which was significantly higher than that of other diseases in department of neurosurgery. The top three of intracranial tumors in children in our hospital in recent five years were respectively craniopharyngioma, accounted for 20.34%, gliomas, account-

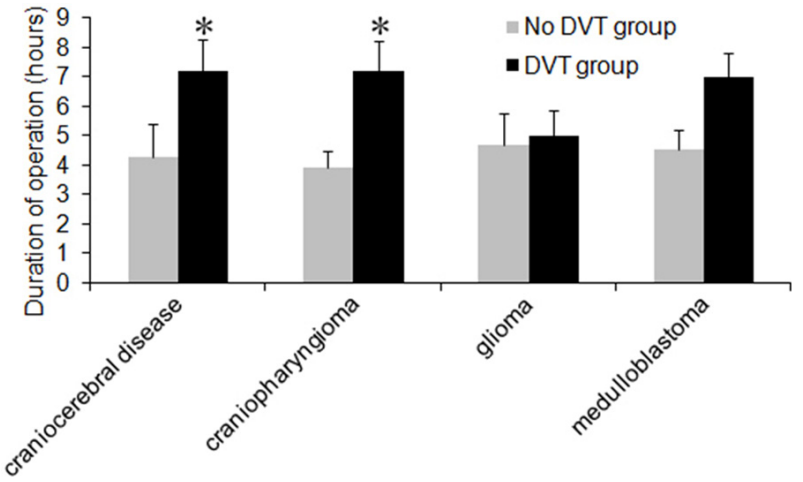

Figure 1. Comparison of operation time between the two groups of patients. *$P<0.05$, compared with non DTV group.

ed for 19.60%, and medulloblastomas, accounted for 12.38%.

The relationship between DVT and operation time

The occurrence of DVT in children is related to the CVC indwelling, and the time of indwelling may be the influencing factors of thrombosis. Therefore, we calculated the average operation time of the two groups of patients. As shown in **Figure 1**, the average operation time in pediatric neurosurgery was 4.29 hours, and the average operation time of the children DTV was 7.2 hours, which had a significant difference. The average operation time of the same disease among the three the most common tumors in department of pediatric neurosurgery were compared. The results showed that the average operation time of craniopharyngioma but non children DVT group was 3.9 hours, of children DVT group was 7.2 hours, which also had a significant difference. The average operation time of medulloblastoma but non children DVT group was 4.5 hours, of children DVT children was 7 hours. The average operation time of glioma but non children DVT group was 4.7 hours, of children DVT was 5 hours. Due to each of the latter two groups had only one case, they were not undergone statistical analysis. Because the CVC indwelling was performed throughout the operation process, the long time operation meaned long time of CVC indwelling and the opportunities of thrombosis was increased.

The relationship between DVT and D-two dimer

When the ultrasound diagnosis of DVT was performed, the D-dimer was detected at the same time, which found that 11 cases of D-two dimer were increased in 18 of children with DVT (three cases were tested without D-dimer examination), suggesting the acute thrombosis. 4 cases of two D-dimer were negative, suggesting the non acute thrombosis. Ultrasound examination of all the D-dimer negative children were suggestive of the turgid type iliac femoral venous thrombosis, and D-dimer was no longer increased, indicating the time of thrombus formation be relatively long. Therefore, the time that found or diagnosed of thrombosis is not necessarily the thrombus formation time.

The interval from postoperation to the diagnosis of DVT

The interval from postoperation to the diagnosis of DVT, except for 1 case was diagnosed of DVT during operation, most of the rest DTVs occurred in 10 days after operation. 3 cases of DVT patients were not performed operation during this time, which were not undergone statistics.

Discussion

Children are not susceptible to DVT, but once DVT occurs in children, which is easily complicated by pulmonary embolism and the mortality is 1%-4% [7]. PTS can cause venous insufficiency and affect seriously the children's activities and daily life. So it is necessary to investigate the incidence of DVT in children. At present, there is no literature about the incidence of DVT in Children neurosurgery [8]. The statistical analysis of the data of past five years in Children neurosurgery in our hospital was completed, it was found that the annual incidence of DVT was 36.3/10000 in department of pediatric neurosurgery of our hospital. The literatures showed that the incidence of children DVT in

hospitalized was 5/10000, the incidence of DVT in pediatric ICU was 24/10000 [9]. The incidence of children DVT in our hospital was higher than that of the literatures [10], which may be due to the following possible causes. First of all, most of the diseases in department of neurosurgery of our hospital were tumors of the central nervous system. While the literature reports on statistical analysis of 137 cases children with DVT found that children cancer accounted for 22.6%, and the second two related conditions were congenital heart disease and trauma [11, 12], indicating that the tumor is the important cause of children thrombosis [13].

In recent five years, only one case of all 18 cases with postoperative children DVT in department of Neurosurgery of our hospital was non tumor patient, indicating that the concentrated tumor diseases of children may be one of the reasons for high incidence of children DVT. Secondly, the children operations in our hospital were indwelled CVC for intraoperative transfusion, blood transfusion and anesthesia administration. It is showed that CVC is an important independent risk factors among thrombosis in children [14-16], so general indwelling CVC is the reason of high incidence children DVT in our hospital.

In addition, the children diagnosed as DVT were those who the limbs were swelling and DVT was confirmed by the ultrasound in this retrospective study. While the children without typical symptoms and signs of thrombosis were not included in the statistics, so the incidence of children DVT in neurosurgery was actually higher. CVC related thrombosis in children often lacks the obvious clinical symptoms and signs. So the screening program may find out more children DVT patients.

The formation of children thrombosis also follows the three factors of Virchow thrombosis. But the children are not susceptible to DVT because of the characteristics of children's physiology, and there are three reasons: 1. the children have lower capacity of generating thrombin than the adult, 2. α2 globulins in children has higher ability of inhibition of thrombin than in adult, 3. the venous wall in children has stronger antithrombotic ability than in adult. The factors that may trigger the DVT are divided into primary and secondary. The primary factors mostly are abnormal gene, protein C, protein S deficiency and hyperhomocysteinemia [17]. Secondary factors includs CVC, infection, operation, parenteral nutrition, heart disease, malignant tumor chemotherapy, bone marrow transplantation, in which CVC is the most common secondary factors [11]. All children DVT in our study occurred in proximal or deep vein of the lower extremity indwelling CVC, suggesting that the occurrence of DVT is related to CVC [18].

If the formation of children DVT is only interpreted with CVC factor, children DVT should be averagely occured in the neurosurgery disease. We performed a survey of nearly five years of patients with intracranial tumors, and the top three were respectively craniopharyngioma (20.34%), gliomas (19.60%) and medulloblastomas (12.38%). At present, no data showed the relationship between the primary disease of nervous system and children DVT, so we analyzed the relationship between nervous system and children DVT in department of neurosurgery of our hospital, which showed that the primary diseases of DVT children were mostly craniopharyngioma (**Table 3**), up to 66.7%. It is showed that craniopharyngioma accounts for 6-10% of brain tumors in children [19], and the hypopituitarism is often appeared after operation which requires the use of hormone replacement therapy, and the hormone replacement treatment may induce the thrombosis [20, 21]. In addition, although the craniopharyngioma is a benign disease, it is easy to relapse. The operation of recurrent tumor is difficult and need long operation time, resulting in long time of CVC indwelling time, which may also be the reason that it is easy to form the thrombus. Therefore, there is a certain relationship with the primary disease and the thrombosis.

The statistical analysis of operation time showed that the operation time of children DVT group was significantly longer than that of the non DVT group and the longer the operation time meaned the longer the CVC indwelling time. CVC indwelling is the cause of formation of endothelial injury. The thrombosis is caused by vascular endothelial injury, and long time of CVC indwelling may more easily increase the thrombosis caused by the vascular endothelial injury [22]. Therefore, the prolonging of operation time is the factor of formation of children DVT.

This study showed that the thrombosis of majority of children came into being in postoperative 10 days and the majority of the D-dimer were positive. Thsese suggest that DVT screening in pediatric neurosurgery should be in 10 days after operation, and the D-dimer can be the preferred screening indicator. If the D-dimer is increased, the further color Doppler ultrasound examination should be performed to confirm the diagnosis.

To sum up, the causes of lower extremity DVT in children of neurosurgery are in many aspects that include CVC reason, and are related to the primary disease of neurosurgery and the operation time, which is consistent with the previous reports that the formation of children's thrombosis was of a multi factor [14]. Because the cases of the retrospective study are less, it is not sufficient to perform regression analysis of the etiology, which need more clear evidence in further prospective controlled study. Because of the limited conditions, this study failed to investigate whether the thrombosis in patients is associated with pulmonary embolism, it is lack of statistical data of incidence of pulmonary embolism in children DVT in neurosurgery. So the further researchs are need in further study.

Disclosure of conflict of interest

None.

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